Contribution of mammography to MRI screening in BRCA mutation carriers by BRCA status and age

Phi, Xuan-Anh; Saadatmand, Sepideh; De Bock, Geertruida H.; Warner, Ellen; Sardanelli, Francesco; Leach, Martin O.; Riedl, Christopher C.; Trop, Isabelle; Hooning, Maartje J.; Mandel, Rodica

Published in:
British Jounal of Cancer

DOI:
10.1038/bjc.2016.32

Publication date:
2016

FULL PAPER

BJC

British Journal of Cancer (2016) 114, 631–637 | doi: 10.1038/bjc.2016.32

Keywords: *BRCA1*; *BRCA2*; breast cancer; screening; mammography; MRI

Contribution of mammography to MRI screening in *BRCA* mutation carriers by *BRCA* status and age: individual patient data meta-analysis

Xuan-Anh Phi*[,1], Sepideh Saadatmand[2], Geertruida H De Bock[1], Ellen Warner[3], Francesco Sardanelli[4], Martin O Leach[5], Christopher C Riedl[6], Isabelle Trop[7], Maartje J Hooning[8], Rodica Mandel[3], Filippo Santoro[9], Gek Kwan-Lim[5], Thomas H Helbich[6], Madeleine MA Tilanus-Linthorst[10], Edwin R van den Heuvel[11] and Nehmat Houssami[12]

[1]Department of Epidemiology, University of Groningen, University Medical Center Groningen, Postbus 30 001, 9700RB Groningen, The Netherlands; [2]Department of Surgical Oncology, Erasmus University Medical Center Rotterdam, Groene Hilledijk 301, 3075EA Rotterdam, The Netherlands; [3]Department of Medicine, Division of Medical Oncology, Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview Avenua, Toronto, ON, Canada M4N 3M5; [4]On behalf of the HIBCRIT-1 Study, Department of Biomedical Sciences for Health, University of Milan School of Medicine, Scientific Institute (IRCCS) Policlinico San Donato, Unit of Radiology, Via Morandi 30, San Donato Milanese, Milan 20097, Italy; [5]On behalf of the MARIBS Study, CRUK Cancer Imaging Centre at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, 123 Old Brompton Road, London SW7 3RP, UK; [6]Department of Biomedical Imaging and Image-guided Therapy, Division of Molecular and Gender Imaging, Medical University Vienna, Spitalgasse 23 Vienna 1090, Austria; [7]Department of Radiology, Breast Imaging Division, Centre Hospitalier of the University of Montreal (CHUM), Montreal, Tour viger, Pavillion R, 900 Saint Denis Street, Montreal, QC, Canada H2X 0A9; [8]Department of Medical Oncology, Family Cancer Clinic, Erasmus MC Cancer Institute, Groene Hilledijk 301, 3075EA Rotterdam, The Netherlands; [9]On behalf of the HIBCRIT-1 Study, Department of Cell Biology and Neurosciences, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy; [10]On behalf of MRISC Study, Department of Surgical Oncology, Erasmus University Medical Center Rotterdam, Groene Hilledijk 301, 3075EA Rotterdam, The Netherlands; [11]Department of Mathematics and Computer Science, Eindhoven University of Technology, Den Dolech 2, 5600 MB Eindhoven, The Netherlands and [12]Screening and Test Evaluation Program (STEP), School of Public Health, Sydney Medical School, The University of Sydney, Edward Ford Building (A27), Sydney, NSW 2006, Australia

Background: We investigated the additional contribution of mammography to screening accuracy in *BRCA1/2* mutation carriers screened with MRI at different ages using individual patient data from six high-risk screening trials.

Methods: Sensitivity and specificity of MRI, mammography and the combination of these tests were compared stratified for *BRCA* mutation and age using generalised linear mixed models with random effect for studies. Number of screens needed (NSN) for additional mammography-only detected cancer was estimated.

Results: In *BRCA1/2* mutation carriers of all ages (BRCA1 = 1219 and BRCA2 = 732), adding mammography to MRI did not significantly increase screening sensitivity (increased by 3.9% in *BRCA1* and 12.6% in *BRCA2* mutation carriers, $P > 0.05$). However, in women with *BRCA2* mutation younger than 40 years, one-third of breast cancers were detected by mammography only. Number of screens needed for mammography to detect one breast cancer not detected by MRI was much higher for *BRCA1* compared with *BRCA2* mutation carriers at initial and repeat screening.

Conclusions: Additional screening sensitivity from mammography above that from MRI is limited in *BRCA1* mutation carriers, whereas mammography contributes to screening sensitivity in *BRCA2* mutation carriers, especially those ⩽40 years. The evidence from our work highlights that a differential screening schedule by *BRCA* status is worth considering.

*Correspondence: X-A Phi; E-mail: x.a.phi@umcg.nl

Received 24 July 2015; revised 17 December 2015; accepted 25 January 2016; published online 23 February 2016

Women with a *BRCA1* or *BRCA2* mutation have limited choices to prevent mortality resulting from their 40–80% lifetime risk for breast cancer (Chen and Parmigiani, 2007). Screening with yearly MRI from age 25 years onwards, and additional mammography from age 30 years is recommended in international guidelines (Mann *et al*, 2008; Sardanelli *et al*, 2010; Zonderland *et al*, 2012; NICE, 2013), and is estimated to be slightly less effective than preventive mastectomy (Kurian *et al*, 2010; Heemskerk-Gerritsen *et al*, 2013). Several prospective high-risk screening studies have evaluated both MRI and mammography (Lord *et al*, 2007; Warner *et al*, 2008) as a screening strategy in high-risk women to improve screening sensitivity. In the absence of randomised controlled trials for MRI screening, these screening studies build on evidence that early detection of breast cancer may confer benefit as shown for mammography in population screening (Glasziou and Houssami, 2011). The combination of mammography and MRI screening of *BRCA1/2* carriers in most guidelines, from the age of 30 or 40 years (Mann *et al*, 2008; Sardanelli *et al*, 2010; Zonderland *et al*, 2012; NICE, 2013), is based on the enhanced sensitivity shown through this strategy (Lord *et al*, 2007; Warner *et al*, 2008), despite arguments around limitations of mammography. These include that mammography is relatively sensitive in fatty breasts (generally in older women) but less sensitive in young women who frequently have dense breasts. In addition, screening with mammography could lead to the induction of breast cancer by X-rays at younger ages (Jansen-van der Weide *et al*, 2010). Proper repair of DNA double-strand breaks that are caused by low-dose X-rays is impaired at any age in both *BRCA1* and *BRCA2* mutations carriers (Powell and Kachnic, 2003). This makes *BRCA1* and *BRCA2* mutation carriers more susceptible than non-carriers, possibly also at older ages, to the cumulative effect of yearly mammograms. Given these potential disadvantages of mammography, it is important to balance the potential benefits and harms of mammography screening in *BRCA1/2* mutation carriers. Hence, substantial early detection of breast cancer by mammography is needed to outweigh the potential harm of cancer induction (Jansen-van der Weide *et al*, 2010) in *BRCA1/2* mutation carriers.

We performed an individual patient data (IPD) meta-analysis from six prospective MRI screening studies to determine if mammography screening in *BRCA1/2* mutation carriers in addition to MRI improves screening accuracy, and whether this effect differs between *BRCA1* and *BRCA2* gene mutation carriers or by different age groups.

MATERIALS AND METHODS

An IPD meta-analysis was conducted by pooling individual data from relevant prospective MRI screening studies (Phi *et al*, 2014). Studies were eligible if mammography and MRI breast cancer sensitivity and specificity were compared in women with a *BRCA1/2* mutation. After searching PubMed, 12 studies met the eligibility requirements and were sought to contribute to the data (Phi *et al,* 2014). Six of these provided IPD data (Leach *et al*, 2005; Rijnsburger *et al*, 2010; Trop *et al*, 2010; Sardanelli *et al*, 2011; Passaperuma *et al*, 2012; Riedl *et al*, 2015), and were included in this meta-analysis; the reasons for non-inclusion of some studies have been reported in our earlier work (Phi *et al*, 2014). Included studies were assessed in terms of reporting quality, and were qualified as high quality (Phi *et al*, 2014). The data were assembled and cross-checked with the original publications; inclusion criteria for analyses were women with a *BRCA1/2* mutation, screened annually with both mammography and MRI. Breast cancer diagnosis was confirmed by pathology and the absence of breast cancer at 1 year follow-up (Phi *et al,* 2014). A summary of the included studies was reported previously (http://jco.ascopubs.org/content/33/4/349/T1.large.jpg)

Primary outcome and definition. Primary outcome was sensitivity and specificity of mammography and MRI separately, as well as combined. Analyses were stratified for mutation type (*BRCA1* or *BRCA2*) and age in years at screening (40 years and younger, between 41 and 50 years, over 50 years).

Sensitivity was defined as the number of breast cancers detected by a screening modality (MRI or mammography, or the combination) from the total number of breast cancers diagnosed during the study course. Specificity of a screening modality was defined as the number classified as true negative by the test from the total number of true-negative plus false-positive results.

A true positive was defined as a positive screening result (BI-RADS 0, 3, 4, 5) followed by a pathology-proven breast cancer. A false positive was defined as a positive screening result (BI-RADS 0, 3, 4, 5) not followed by a pathology-proven breast cancer within 1 year of follow-up. A true negative was defined as a negative screening result (BI-RADS 1, 2) not followed by pathology-proven breast cancer within 1 year of follow-up. A false-negative case was defined as a negative screening result (BI-RADS 1, 2) followed by a pathology-proven breast cancer within 1 year of follow-up.

Statistical analysis. Stratified by *BRCA* status and age group, descriptive statistics of the characteristics of the women and their breast cancer were provided. Breast cancer incidence was calculated per 1000 woman-years. The related 95% confidence intervals (CIs) were computed, assuming the incidence follows a Poisson distribution. To compare differences between groups in proportion of DCIS, invasive tumour size and grade, χ^2 tests or Fisher's exact tests were applied.

To estimate the sensitivity and the specificity of the screening modalities, repeated screening results were summarised to form binomial counts for each woman. For each woman, the number of true-positive and true-negative screens per modality, and the number of total screening visits with or without breast cancer detected were counted. In this way, binomial counts per modality were calculated and analysed, taking into account that each woman was her own control. As the dependent variable was assumed to follow a binomial distribution, a generalised linear mixed model with logit link function was applied, and the binomial proportions were modelled as a function of modality and *BRCA* status and conducted separately for sensitivity and specificity. Studies were entered as random-effect variables and study heterogeneities were assumed to depend on modality. The analyses were conducted separately for each age group. To test the differences between the sensitivities and specificities for the three modalities, Wald tests were applied, where the hypothesis was that the difference between the two proportions under study was 0.

The number of mammographic screens that would have been needed (NSN) to detect one breast cancer that was missed by MRI was calculated, and stratified according to BRCA mutation, age group and screening round (first or subsequent round). All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). *P*-values <0.05 were considered statistically significant.

RESULTS

Study population and breast cancer characteristic. The analyses were based on 1951 *BRCA1/2* mutation carriers with 6085 woman-years of follow-up (Table 1). There was no significant difference in cancer risk between *BRCA1* and *BRCA2* mutation carriers.

Five breast cancers were diagnosed before the age of 30 in *BRCA1* mutation carriers, and none in *BRCA2* mutation carriers. The proportion of DCIS differed between BRCA groups in age groups older than 40 years, as shown in Table 1.

Sensitivity and specificity of MRI and mammography in BRCA1 mutation carriers. In *BRCA1* mutation carriers, there were no

Table 1. Overview of women ($n = 1951$) and their BCs ($n = 184$)[a]

	All ages		Age ⩽40 years		Age 41–50 years		Age over 50 years	
	BRCA1	***BRCA2***	***BRCA1***	***BRCA2***	***BRCA1***	***BRCA2***	***BRCA1***	***BRCA2***
Women (*N*)	1219	732	605	301	482	308	310	228
Follow-up time (woman-years)	3840	2245	1691	749	1216	812	895	673
BC (*N*)	112	72	46	18	38	37	28	17
BC risk ((95% CI)	29.2 (24–35.1)	32.1 (25.1–.40.4)	27.2 (19.9–36.3)	24 (14.2–38)	31.3 (22.1–42.9)	45.6 (32.1–62.8)	31.3 (20.8–45.2)	25.3 (14.7–40.4)
DCIS[b]	15 (13.4%)	22 (30.6%)	9 (19.6%)	3 (16.7%)	3 (7.9%)	13 (35.1%)	3 (10.7%)	6 (35.3%)
Invasive cancers[c]	97 (86.6%)	50 (69.4%)	37 (80.4%)	15 (83.3%)	35 (92.1%)	24 (64.9%)	25 (89.3%)	11 (64.7%)
Invasive <1 cm	26 (26.8%)	17 (34.0%)	8 (21.6%)	2 (13.3%)	10 (28.6%)	11 (45.8%)	8 (32.0%)	4 (36.4%)
Invasive 1–2 cm	35 (36.1%)	12 (24.0%)	13 (35.1%)	5 (33.3%)	8 (22.9%)	3 (12.5%)	14 (56.0%)	4 (36.4%)
Grade 1	7 (7.2%)	5 (10.0%)	1 (2.7%)	0 (–)	4 (11.4%)	3 (12.5%)	2 (8.0%)	2 (18.2%)
Early-stage tumour (DCIS or invasive <1 cm)	41(36.6%)	39 (54.2%)	17 (37.0%)	5 (27.8%)	13 (34.2%)	24 (64.9%)	11 (39.3%)	10 (58.8%)

Abbreviations: BC = breast cancer; DCIS = ductal carcinoma *in situ*. BC risk was expressed per 1000 woman-years of follow-up.
[a]Stratified by age at screening and for *BRCA1* or *BRCA2* mutation status
[b]$P = 0.0095$ comparing DCIS rate between *BRCA1* and *BRCA2* mutation carriers at the age 41–50 years, and for all ages, comparing DCIS rate between *BRCA1* and *BRCA2* mutation carriers, $P = 0.0077$.
[c]Nine cases with missing histological subtype were considered as invasive BCs.

Table 2. Sensitivity and specificity of screening modalities[a]

		Mammography			MRI			Combination		
Age group (years)	**Mutation status**	**No. of BC detected**	**Sensitivity (%) (95% CI)**	**Specificity (%) (95% CI)**	**No. of BC detected**	**Sensitivity (%) (95% CI)**	**Specificity (%) (95% CI)**	**No. of BC detected**	**Sensitivity (%) (95% CI)**	**Specificity (%) (95% CI)**
All ages	*BRCA1* (n = 112)	39	35.7 (25.9–46.9)	93.8 (89.3–96.5)	92	88.6 (73.4–95.6)	84.4 (78.7–88.8)	98	92.5 (80.1–97.4)	80.4 (72.8–86.2)
	BRCA2 (n = 72)	31	44.6 (31.9–58)	93.4 (88.4–96.3)	53	80.1 (58.9–91.9)	85.3 (79.6–89.6)	64	92.7 (79.3–97.7)	80.5 (72.8–86.4)
⩽40	*BRCA1* (n = 46)	18	39.1 (26.2–53.9)	94.9 (91.2–97.1)	34	77.5 (57–90)	84.3 (78.7–88.7)	38	86.8 (63.1–96.2)	81 (73.9–86.5)
	BRCA2 (n = 18)	10	55.6 (32.9–76.1)	92.3 (86.6–95.7)	9	52.7 (27.2–76.8)	80.2 (72.9–85.8)	15	87.2 (56.1–97.3)	75.3 (66.6–82.4)
41–50	*BRCA1* (n = 38)	13	34.2 (21–50.5)	91.5 (86.7–94.6)	34	93.1 (70.8–98.7)	82.9 (77.9–87)	35	94.1 (74.5–98.9)	77.2 (70.5–82.8)
	BRCA2 (n = 38)	14	37.8 (22.7–55.5)	92 (87–95.2)	30	86.4 (58.2–96.7)	86 (81.1–89.8)	33	91.2 (70.4–97.9)	80 (73.3–85.3)
>50	*BRCA1* (n = 28)	8	29.4 (12.8–54.2)	96.8 (91.9–98.8)	24	89.1 (54.8–98.2)	89.9 (82.6–94.3)	25	89.3 (71.3–96.6)	87.4 (79.3–92.6)
	BRCA2 (n = 17)	7	45.5 (19.3–74.4)	97.4(92.8–99.1)	14	85 (43.7–97.7)	91.1 (84–95.2)	16	94.1 (67.5–99.2)	88.6 (80.7–93.6)

Abbreviations: BC = breast cancer; CI = confidence interval; MRI = magnetic resonance imaging.
[a]Stratified by age at screening and by *BRCA1* or *BRCA2* mutation status.

statistically significant differences in sensitivity and specificity between mammography and MRI combined compared with MRI alone. Sensitivity of the combination was higher compared with that of MRI alone in all age groups (age ⩽40: 86.8% (63.1–96.2) *vs* 77.5% (57–90), $P = 0.441$; age 41–50: 94.1% (74.5–98.9) *vs* 93.1% (70.8–98.7), $P = 0.895$; age >50: 89.3% (71.3–96.6) *vs* 89.1% (54.8–98.2), $P = 0.986$). Combining mammography and MRI decreased specificity compared with MRI screening alone in all age groups (age ⩽40 years: 81% (73.9–86.5) *vs* 84.3% (78.7–88.7), $P = 0.409$; age 41–50 years: 77.2% (70.5–82.8) *vs* 82.9% (77.9–87), $P = 0.135$; age >50 years: 87.4% (79.3–92.6) *vs* 89.9% (82.6–94.3), $P = 0.566$). Further results are shown in Table 2.

Sensitivity and specificity of MRI and mammography in *BRCA2* mutation carriers. In *BRCA2* carriers, there were no significant differences in sensitivity or specificity between combined mammography and MRI and MRI alone in all age groups. Sensitivity of the combination was higher compared with that of MRI alone in all age groups (age ⩽40 years: 87.2% (56.1–97.3) *vs* 52.7% (27.2–76.8), $P = 0.075$; age 41–50 years: 91.2% (70.4–97.9) *vs* 86.4% (58.2–96.7), $P = 0.646$; age >50 years: 94.1% (67.5–99.2) *vs* 85% (43.7–97.7), $P = 0.474$). Combining mammography and MRI decreased specificity compared with MRI screening alone in all age groups (age ⩽40 years: 75.3% (66.6–82.4) *vs* 80.2% (72.9–85.8), $P = 0.351$; age 41–50 years: 80% (73.3–85.3) *vs* 86% (81.1–89.8), $P = 0.105$; age >50 years: 88.6% (80.7–93.6) *vs* 91.1% (84–95.2), $P = 0.565$). Further results are shown in Table 2.

Mammography contribution to screening sensitivity in *BRCA1* mutation carriers. In *BRCA1* carriers overall, adding mammography to MRI screening increased sensitivity by roughly 4–92.5% (Table 2) ($P = 0.553$). In the ⩽40 years age group, the addition of mammography increased sensitivity by 9.3% (Table 2). Without mammography, 3 of 46 (6.5%) breast cancers, including 2 DCIS, would not have been detected (Table 3) in this subgroup. In the 41–50 years group, additional mammography increased sensitivity by only 1% (Table 2), detecting 1 DCIS (2.7%) (Table 3). Similarly, in the >50 years age group, mammography detected one additional cancer (3.4% of cancers) (Table 3).

Mammography contribution to screening sensitivity in *BRCA2* mutation carriers. In *BRCA2* carriers, adding mammography to

Table 3. Mammography-only detected breast cancers stratified for *BRCA1* or *BRCA2* mutation status

No.	Mutation status	Age at diagnosis	Tumour type	Invasive tumour size	Invasive tumour grade	Screening round
1	*BRCA1*	31	DCIS	—	—	2
2	*BRCA1*	33	DCIS	—	—	2
3	*BRCA1*	40	IDC	1–2 cm	Grade 3	1
4	*BRCA1*	42	DCIS	—	—	3
5	*BRCA1*	56	IDC	<1 cm	Grade 3	4
1	*BRCA2*	36	DCIS	—	—	1
2	*BRCA2*	37	DCIS	—	—	1
3	*BRCA2*	35	IDC	<1 cm	Grade 2	4
4	*BRCA2*	36	IDC	1–2 cm	Grade 3	1
5	*BRCA2*	37	ILC	2–5 cm	Grade 2	1
6	*BRCA2*	39	Other	NA	NA	3
7	*BRCA2*	42	DCIS	—	—	4
8	*BRCA2*	53	DCIS	—	—	2
9	*BRCA2*	44	ILC	>5 cm	3	1
10	*BRCA2*	47	ILC	>5 cm	2	5
11	*BRCA2*	51	NA	NA	NA	1

Abbreviations: DCIS = ductal carcinoma *in situ*; IDC = invasive ductal; ILC = invasive lobular; NA = not applicable.

Table 4. NSN for one additional mammography-only detected cancer for first and subsequent screening rounds

BRCA	Age group (years)	Number of BC in study subjects	Number of screens	BC only detected by mammography	NSN for mammography to detect one BC missed by MRI
First screening round					
BRCA1	All ages	45	1053	2	527
	Age <40	19	555	2	278
	41–50	14	304	0	NA
	Age >50	12	194	0	NA
BRCA2	All ages	18	564	6	94
	Age <40	10	221	4	55
	41–50	10	204	1	204
	Age >50	8	139	1	139
Subsequent (repeat) screening rounds					
BRCA1	All ages	67	2150	3	717
	Age <40	27	775	1	775
	41–50	23	797	1	797
	Age >50	17	578	1	578
BRCA2	All ages	54	1155	5	231
	Age <40	8	281	2	141
	41–50	27	444	2	222
	Age >50	9	430	1	430

Abbreviations: BC = breast cancer; MRI = magnetic resonance imaging; NA = not applicable; NSN = number of screens needed.

MRI screening increased sensitivity by 12.6–92.7% (Table 2) ($P = 0.154$). In the ⩽40 age group, additional mammography increased sensitivity by 34.5% (Table 2). Without mammography, 6 of 18 cancers (33.3%), including 2 DCIS, would not have been detected in this young age group (Table 3). In women aged 41–50 years, adding mammography nonsignificantly increased sensitivity by nearly 5% (Table 2) and detected 3 cancers, including 1 DCIS, which were not detected by MRI (8.1% of cancers). In the >50 years age group, screening sensitivity increased nonsignificantly by ~9% (Table 2), and mammography detected two cancers (11.8%) that were not detected by MRI, including 1 DCIS.

Number of mammographic screens needed to detect one breast cancer not detected by MRI. For the first screening round, the NSN for mammography to detect one breast cancer not detected by MRI was 527 for women with a *BRCA1* mutation and 94 for women with a *BRCA2* mutation for all ages (Table 4). For subsequent screening rounds, the NSN for mammography to detect an additional breast cancer for women with a *BRCA1* mutation (717 screens) was roughly three times that for women with a *BRCA2* mutation (231 screens).

DISCUSSION

This IPD meta-analysis has identified differences in the contribution of mammography to screening high-risk women according to age and mutation status. Adding mammography to MRI screening in *BRCA1* mutation carriers leads to a very modest increase in sensitivity of 3.9% among 112 breast cancers ($P = 0.553$), and a small decrease in specificity (by 4%, $P = 0.154$). One invasive cancer and 2 DCIS (6.5%) of the 46 *BRCA1* breast cancers detected before the age of 40 years, and only 1 DCIS and 1 invasive cancer <1 cm (3%) in a total of 66 *BRCA1* breast cancers would not have been detected at that screen after the age of 40 years. The percentage of early-stage (DCIS or <1 cm invasive) cancers detected with both MRI and mammography screening of 36.6%

(41 out of 112) would decrease by 3.6% (37 out of 112) if mammography was not be performed. Using combined MRI and mammography, 63.4% of the detected cancers were invasive and >1 cm, with 0.9% of these detected by mammography only. To detect one breast cancer missed by MRI, we estimated that 527 screens for the first screening round and 717 screens for subsequent rounds with mammography would be needed.

The contribution of mammography above MRI to screening sensitivity in the 72 *BRCA2* mutation carriers was 12.6% ($P>0.05$). Additional mammography in *BRCA2* mutation carriers also decreased the specificity. Without mammography one-third of breast cancers would not have been detected in *BRCA2* mutation carriers aged 40 years and younger, but this proportion was 9.3% in those older than 40 years. We estimate that the percentage of *BRCA2* cancers detected at very early stage (DCIS or invasive <1 cm) with combined MRI and mammography screening of 54.2% (39 out of 72) would decrease to 47.2% (34 out of 72) without mammography. Only 94 screens at first round and 231 screens at subsequent rounds of mammography screening are needed to detect a breast cancer missed by MRI. Without mammography, four advanced-stage cancers (4 out of 72 cancers, 5.6%) would have been missed in *BRCA2* carriers. An advantage of mammography over MRI has been the ability to detect DCIS by visualising microcalcifications. The proportion of DCIS is larger for women with a *BRCA2* mutation than for women with a *BRCA1* mutation, thus differences in histology distributions in *BRCA*-associated breast cancers may account for our findings (Heijnsdijk *et al*, 2012). There might also be *BRCA* mutation-specific differences in tumour phenotypes that also contribute to differences in screen detection. The modest additional value of digital-only mammography to current MRI screening of *BRCA1* mutation carriers was recently shown in a retrospective study (Obdeijn *et al*, 2014). Only 2 (2%) DCIS of 94 breast cancers were detected by mammography alone, none in women aged below 40 years and no invasive cancers. Importantly, in this retrospective study with recent data MRI screening detected 67% of the breast cancers detected as DCIS or <1 cm, considerably more than the 41–44% published for the Dutch, UK and Canadian studies of our IPD meta-analyses (Rijnsburger *et al*, 2010; Passaperuma *et al*, 2012; Evans *et al*, 2014) or 36.6% of this IPD meta-analysis.

It could be argued that at the time the studies forming our IPD analyses were conducted, radiologists might not have had extensive experience with breast MRI screening. Most likely, both a learning curve, as expected for any new screening modality, and improved techniques explain the relatively improved MRI sensitivities in more recent studies. A learning curve for MRI screening accuracy in high-risk women was evident for the Canadian study, in particular for DCIS detection (Warner *et al*, 2011). However, in a previous report in this study population (Phi *et al*, 2014), the sensitivity of each of MRI and mammography fluctuated over the years, and heterogeneity was evident across different studies possibly masking any potential effect of timeframe (Phi *et al*, 2014). A cohort study from the Netherlands showed that digital mammography had higher sensitivity compared with studies reporting film mammography (and a transition to digital) (Obdeijn *et al*, 2014). However, in the Italian HIBCRIT-1 Study, transition from film screen to digital mammography (resulting in screening with roughly equal mix of film screen and digital) did not increase mammography sensitivity in high-risk women (Sardanelli *et al*, 2011). Newer mammography technologies such as tomosynthesis (3D mammography), which have better screening sensitivity than standard mammography (Houssami *et al*, 2014), have not yet been compared with MRI screening of *BRCA* carriers. This lacking evidence in high-risk screening is worthy of research effort but would still imply increased ionising radiation from tomosynthesis (Svahn *et al*, 2014).

In contrast to benefits of possible earlier breast cancer detection, there are also possible harmful effects of additional mammography as outlined in the Introduction. Two-fold increase in breast cancers in *BRCA1/2* mutation carriers after exposure to 4 or more radiographs, compared with non-exposure, was significant below age 30 years (HR = 1.9 (95% CI: 1.2–3.0), but not at 30–39 years (Pijpe *et al*, 2012). Two other studies did not demonstrate tumour induction in *BRCA1/2* mutation carriers by screening mammography or low-dose contralateral irradiation from breast-conserving treatment (Pierce *et al*, 2000; Narod *et al*, 2006). However, this may have been because of modest follow-up time in these studies, with consideration that latency time for radiation-induced breast cancer is 10–15 years (Travis *et al*, 2005; Jansen-van der Weide *et al*, 2010).

From two meta-analyses based on retrospective studies, the estimated cumulative risk of breast cancer by the age of 70 years vary from 57% (95% CI: 47–66%) to 65% (95% CI: 44–78) in women with a *BRCA1* mutation and from 45% (95% CI: 31–56%) to 49% (95% CI: 40–57) in women with a *BRCA2* mutation (Antoniou *et al*, 2003; Chen and Parmigiani, 2007). In this IPD meta-analysis, we combined IPD from six prospective studies, making this the largest analysis in the world of prospectively collected screening data on *BRCA1/2* mutation carriers, although numbers are modest in some subgroups. We did not observe a significant difference in the risk of breast cancer between *BRCA1* and *BRCA2* mutation carriers given a relatively small sample of breast cancers in the IPD data set. Although data from six studies could not be included, this only resulted in ~716 women with *BRCA1/2* mutations (36 breast cancers) not being included in the IPD (Kuhl *et al*, 2005, 2010; Lehman *et al*, 2005, 2007; Hagen *et al*, 2007; Weinstein *et al*, 2009). As these studies showed generally similar results for the added value of mammography to MRI, we would not expect their non-inclusion to have substantially altered our estimates.

This work differs from our recent report using the same IPD data (Phi *et al*, 2014) because the present analyses focus on screening outcomes by *BRCA* status and age group to determine mammography's contribution. Based on our findings, the additional detection from mammography in *BRCA1* mutation carriers who receive MRI screening is minimal, and might not outweigh potential disadvantages (potential cancer induction by radiation, false-positive results). It may be reasonable, on the basis of this collective evidence, to consider potential omission of mammography screening in *BRCA1* mutation carriers or to open discussion on its potential omission given its limited contribution. In *BRCA2* mutation carriers, the contribution of mammography above MRI is more evident. Different screening recommendations for these two groups of women defined by *BRCA* mutation status should be considered on the basis of the evidence we report, factoring the estimated contribution of mammography and its potential harms.

ACKNOWLEDGEMENTS

No specific project funding was received. N Houssami receives a National Breast Cancer Foundation (NBCF Australia) Breast Cancer Research Leader Fellowship.

CONFLICT OF INTEREST

The following authors reported consulting or advisory roles: Thomas H Helbich (Siemens; Philips); Francesco Sardanelli (Bayer HealthCare including honoraria; Bracco Imaging including funding; IMS-Giotto including funding); Edwin R van den Heuvel (MSD). The other authors declare no conflict of interest.

REFERENCES

Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Loman N, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles DM, Tang N, Olah E, Anton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski B, Tulinius H, Thorlacius S, Eerola H, Nevanlinna H, Syrjakoski K, Kallioniemi OP, Thompson D, Evans C, Peto J, Lalloo F, Evans DG, Easton DF (2003) Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet* **72**(5): 1117–1130.

Chen S, Parmigiani G (2007) Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol* **25**(11): 1329–1333.

Evans DG, Kesavan N, Lim Y, Gadde S, Hurley E, Massat NJ, Maxwell AJ, Ingham S, Eeles R, Leach MO. MARIBS GroupHowell A, Duffy SW (2014) MRI breast screening in high-risk women: cancer detection and survival analysis. *Breast Cancer Res Treat* **145**(3): 663–672.

Glasziou P, Houssami N (2011) The evidence base for breast cancer screening. *Prev Med* **53**(3): 100–102.

Hagen AI, Kvistad KA, Maehle L, Holmen MM, Aase H, Styr B, Vabo A, Apold J, Skaane P, Moller P (2007) Sensitivity of MRI versus conventional screening in the diagnosis of BRCA-associated breast cancer in a national prospective series. *Breast (Edinburgh, Scotland)* **16**(4): 367–374.

Heemskerk-Gerritsen BA, Menke-Pluijmers MB, Jager A, Tilanus-Linthorst MM, Koppert LB, Obdeijn IM, van Deurzen CH, Collee JM, Seynaeve C, Hooning MJ (2013) Substantial breast cancer risk reduction and potential survival benefit after bilateral mastectomy when compared with surveillance in healthy BRCA1 and BRCA2 mutation carriers: a prospective analysis. *Ann Oncol* **24**(8): 2029–2035.

Heijnsdijk EA, Warner E, Gilbert FJ, Tilanus-Linthorst MM, Evans G, Causer PA, Eeles RA, Kaas R, Draisma G, Ramsay EA, Warren RM, Hill KA, Hoogerbrugge N, Wasser MN, Bergers E, Oosterwijk JC, Hooning MJ, Rutgers EJ, Klijn JG, Plewes DB, Leach MO, de Koning HJ (2012) Differences in natural history between breast cancers in BRCA1 and BRCA2 mutation carriers and effects of MRI screening-MRISC, MARIBS, and Canadian studies combined. *Cancer Epidemiol Biomarkers Prev* **21**(9): 1458–1468.

Houssami N, Macaskill P, Bernardi D, Caumo F, Pellegrini M, Brunelli S, Tuttobene P, Bricolo P, Fanto C, Valentini M, Ciatto S (2014) Breast screening using 2D-mammography or integrating digital breast tomosynthesis (3D-mammography) for single-reading or double-reading – evidence to guide future screening strategies. *Eur J Cancer (Oxford, England: 1990)* **50**(10): 1799–1807.

Jansen-van der Weide MC, Greuter MJ, Jansen L, Oosterwijk JC, Pijnappel RM, de Bock GH (2010) Exposure to low-dose radiation and the risk of breast cancer among women with a familial or genetic predisposition: a meta-analysis". *Eur Radiol* **20**(11): 2547–2556.

Kuhl C, Weigel S, Schrading S, Arand B, Bieling H, Konig R, Tombach B, Leutner C, Rieber-Brambs A, Nordhoff D, Heindel W, Reiser M, Schild HH (2010) Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. *J Clin Oncol* **28**(9): 1450–1457.

Kuhl CK, Schrading S, Leutner CC, Morakkabati-Spitz N, Wardelmann E, Fimmers R, Kuhn W, Schild HH (2005) Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. *J Clin Oncol* **23**(33): 8469–8476.

Kurian AW, Sigal BM, Plevritis SK (2010) Survival analysis of cancer risk reduction strategies for BRCA1/2 mutation carriers. *J Clin Oncol* **28**(2): 222–231.

Leach MO, Boggis CR, Dixon AK, Easton DF, Eeles RA, Evans DG, Gilbert FJ, Griebsch I, Hoff RJ, Kessar P, Lakhani SR, Moss SM, Nerurkar A, Padhani AR, Pointon LJ, Thompson D, Warren RM. MARIBS Study Group (2005) Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). *Lancet* **365**(9473): 1769–1778.

Lehman CD, Blume JD, Weatherall P, Thickman D, Hylton N, Warner E, Pisano E, Schnitt SJ, Gatsonis C, Schnall M, DeAngelis GA, Stomper P, Rosen EL, O'Loughlin M, Harms S, Bluemke DA. International Breast MRI Consortium Working Group (2005) Screening women at high risk for breast cancer with mammography and magnetic resonance imaging. *Cancer* **103**(9): 1898–1905.

Lehman CD, Isaacs C, Schnall MD, Pisano ED, Ascher SM, Weatherall PT, Bluemke DA, Bowen DJ, Marcom PK, Armstrong DK, Domchek SM, Tomlinson G, Skates SJ, Gatsonis C (2007) Cancer yield of mammography, MR, and US in high-risk women: prospective multi-institution breast cancer screening study. *Radiology* **244**(2): 381–388.

Lord SJ, Lei W, Craft P, Cawson JN, Morris I, Walleser S, Griffiths A, Parker S, Houssami N (2007) A systematic review of the effectiveness of magnetic resonance imaging (MRI) as an addition to mammography and ultrasound in screening young women at high risk of breast cancer. *Eur J Cancer (Oxford, England: 1990)* **43**(13): 1905–1917.

Mann RM, Kuhl CK, Kinkel K, Boetes C (2008) Breast MRI: guidelines from the European Society of Breast Imaging. *Eur Radiol* **18**(7): 1307–1318.

Narod SA, Lubinski J, Ghadirian P, Lynch HT, Moller P, Foulkes WD, Rosen B, Kim-Sing C, Isaacs C, Domchek S, Sun P. Hereditary Breast Cancer Clinical Study Group (2006) Screening mammography and risk of breast cancer in BRCA1 and BRCA2 mutation carriers: a case–control study. *Lancet Oncol* **7**(5): 402–406.

NICE (2013) CG 164 Familial breast cancer: *NICE Guidance*. Available at http://guidance.nice.org.uk/CG164/NICEGuidance/pdf/English (last accessed 23 September 2013).

Obdeijn IM, Winter-Warnars GA, Mann RM, Hooning MJ, Hunink MG, Tilanus-Linthorst MM (2014) Should we screen BRCA1 mutation carriers only with MRI? A multicenter study. *Breast Cancer Res Treat* **144**(3): 577–582.

Passaperuma K, Warner E, Causer PA, Hill KA, Messner S, Wong JW, Jong RA, Wright FC, Yaffe MJ, Ramsay EA, Balasingham S, Verity L, Eisen A, Curpen B, Shumak R, Plewes DB, Narod SA (2012) Long-term results of screening with magnetic resonance imaging in women with BRCA mutations. *Br J Cancer* **107**(1): 24–30.

Phi X, Houssami N, Obdeijn I, Warner E, Sardanelli F, Leach MO, Riedl CC, Trop I, Tilanus-Linthorst MM, Mandel R, Santoro F, Kwan-Lim G, Helbich TH, de Koning HJ, Van den Heuvel ER, de Bock GH (2014) Magnetic resonance imaging improves breast screening sensitivity in BRCA mutation carriers age $>/=50$ years: evidence from an individual patient data meta-analysis. *J Clin Oncol* **33**(4): 349–356.

Pierce LJ, Strawderman M, Narod SA, Oliviotto I, Eisen A, Dawson L, Gaffney D, Solin LJ, Nixon A, Garber J, Berg C, Isaacs C, Heimann R, Olopade OI, Haffty B, Weber BL (2000) Effect of radiotherapy after breast-conserving treatment in women with breast cancer and germline BRCA1/2 mutations. *J Clin Oncol* **18**(19): 3360–3369.

Pijpe A, Andrieu N, Easton DF, Kesminiene A, Cardis E, Nogues C, Gauthier-Villars M, Lasset C, Fricker JP, Peock S, Frost D, Evans DG, Eeles RA, Paterson J, Manders P, van Asperen CJ, Ausems MG, Meijers-Heijboer H, Thierry-Chef I, Hauptmann M, Goldgar D, Rookus MA, van Leeuwen FE. GENEPSO, EMBRACE, HEBON (2012) Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations: retrospective cohort study (GENE-RAD-RISK). *BMJ (Clin Res Ed.)* **345**: e5660.

Powell SN, Kachnic LA (2003) Roles of BRCA1 and BRCA2 in homologous recombination, DNA replication fidelity and the cellular response to ionizing radiation. *Oncogene* **22**(37): 5784–5791.

Riedl CC, Luft N, Bernhart C, Weber M, Bernathova M, Tea MK, Rudas M, Singer CF, Helbich TH (2015) Triple-modality screening trial for familial breast cancer underlines the importance of magnetic resonance imaging and questions the role of mammography and ultrasound regardless of patient mutation status, age, and breast density. *J Clin Oncol* **33**(10): 1128–1135.

Rijnsburger AJ, Obdeijn IM, Kaas R, Tilanus-Linthorst MM, Boetes C, Loo CE, Wasser MN, Bergers E, Kok T, Muller SH, Peterse H, Tollenaar RA, Hoogerbrugge N, Meijer S, Bartels CC, Seynaeve C, Hooning MJ, Kriege M, Schmitz PI, Oosterwijk JC, de Koning HJ, Rutgers EJ, Klijn JG (2010) BRCA1-associated breast cancers present differently from BRCA2-associated and familial cases: long-term follow-up of the Dutch MRISC Screening Study. *J Clin Oncol* **28**(36): 5265–5273.

Sardanelli F, Boetes C, Borisch B, Decker T, Federico M, Gilbert FJ, Helbich T, Heywang-Kobrunner SH, Kaiser WA, Kerin MJ, Mansel RE, Marotti L, Martincich L, Mauriac L, Meijers-Heijboer H, Orecchia R, Panizza P, Ponti A, Purushotham AD, Regitnig P, Del Turco MR, Thibault F, Wilson R (2010) Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. *Eur J Cancer (Oxford, England: 1990)* **46**(8): 1296–1316.

Sardanelli F, Podo F, Santoro F, Manoukian S, Bergonzi S, Trecate G, Vergnaghi D, Federico M, Cortesi L, Corcione S, Morassut S, Di Maggio C, Cilotti A, Martincich L, Calabrese M, Zuiani C, Preda L, Bonanni B, Carbonaro LA, Contegiacomo A, Panizza P, Di Cesare E, Savarese A, Crecco M, Turchetti D, Tonutti M, Belli P, Maschio AD. High Breast Cancer Risk Italian 1 (HIBCRIT-1) Study (2011) Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the High Breast Cancer Risk Italian 1 Study): final results. *Invest Radiol* **46**(2): 94–105.

Svahn TM, Houssami N, Sechopoulos I, Mattsson S (2014) Review of radiation dose estimates in digital breast tomosynthesis relative to those in two-view full-field digital mammography. *Breast (Edinburgh, Scotland)* **24**(2): 93–99.

Travis LB, Hill D, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, Glimelius B, Andersson M, Pukkala E, Lynch CF, Pee D, Smith SA, Van't Veer MB, Joensuu T, Storm H, Stovall M, Boice Jr JD, Gilbert E, Gail MH (2005) Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. *J Natl Cancer Inst* **97**(19): 1428–1437.

Trop I, Lalonde L, Mayrand MH, David J, Larouche N, Provencher D (2010) Multimodality breast cancer screening in women with a familial or genetic predisposition. *Curr Oncol (Toronto, ON)* **17**(3): 28–36.

Warner E, Causer PA, Wong JW, Wright FC, Jong RA, Hill KA, Messner SJ, Yaffe MJ, Narod SA, Plewes DB (2011) Improvement in DCIS detection rates by MRI over time in a high-risk breast screening study. *Breast J* **17**(1): 9–17.

Warner E, Messersmith H, Causer P, Eisen A, Shumak R, Plewes D (2008) Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. *Ann Intern Med* **148**(9): 671–679.

Weinstein SP, Localio AR, Conant EF, Rosen M, Thomas KM, Schnall MD (2009) Multimodality screening of high-risk women: a prospective cohort study. *J Clin Oncol* **27**(36): 6124–6128.

Zonderland HM, van Vegchel T, van Asperen CJ, Benraadt J, de Bock GH, den Heeten GJ, Rutgers EJT, Smit-Hoeksma GM, Strobbe LJA, van Tienhoven G, Tuut MK, Westenend PJ, Wittenberg J (2012) 13-02-2012-last update, Richtlijn mammacarcinoom (Breast Cancer National Guideline). Available at http://richtlijnendatabase.nl/en/richtlijn/breast_cancer/screening.html (last accessed 10 February 2016).